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(54) Title: STABILIZED PHARMACEUTICAL COMPOSITIONS AND PROCESS FOR THE PREPARATION THEREOF

(57) Abstract

The invention relates to pharmaceutical compositions of enalapril maleate stabilized by maleic acid.

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Stabilized pharmaceutical compositions and process for the preparation thereof

The present invention relates to novel stabilized pharmaceutical compositions, process for their preparation and the use of maleic acid as a stabilizer. The active ingredient of the above compositions is enalapril maleate which is a potent angiotensin-converting enzyme inhibitor, and it is useful in the treatment of hypertension.

Enalapril, its salts and the process for their preparation are described in the European Patent Application publ. No. EP-012401 A1.

As it is known, many compounds that inhibit ACE (Angiotensin-Converting Enzyme) have poor stability either in form of free acids or salts if they are in a pharmaceutical dosage form. These compounds easily decompose first of all by hydrolysis and intramolecular cyclization, but the amount of other decomposition products not identified in many cases may be also significant. This is particularly true in case of enalapril and its maleate salt.

Main decomposition products of enalapril are shown in Fig. demonstrating that the decomposition is due to hydrolytic and cyclization processes.

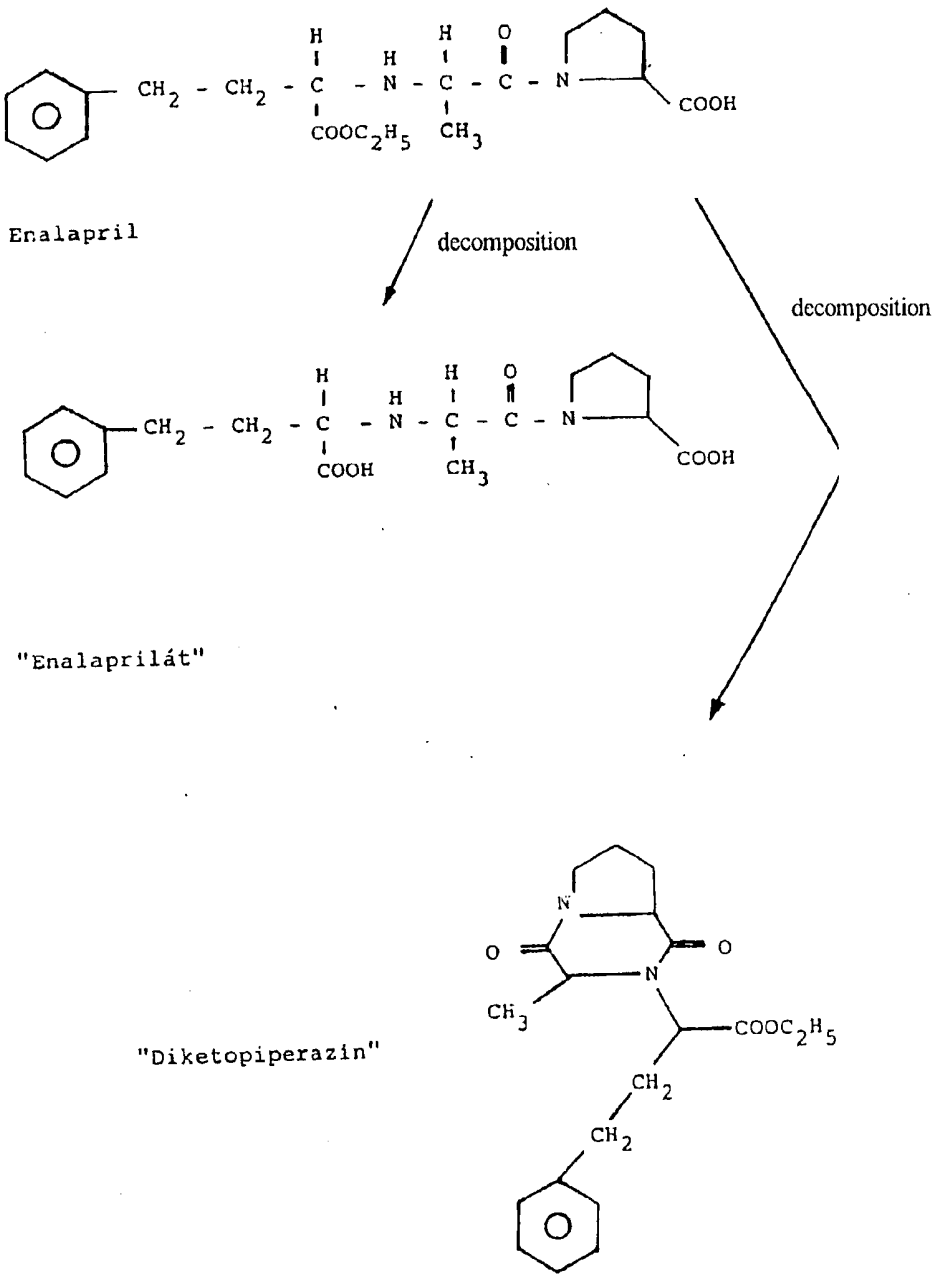
The diketopiperazine (DPK) is the internal cyclization product and the diacid (enalaprilat ET) is the product of ester hydrolysis.

A lot of solutions have been elaborated to stabilize angiotensin-converting enzyme inhibitors, among them enalapril salts in pharmaceutical compositions.

According to the European Patent Application publ. no. EP-0 280 999 A2, magnesium carbonate shows a stabilizing effect in pharmaceutical products containing saccharides, e.g. lactose and quinapril.

According to the European Patent Application publ. no. EP-0 545 194 A1, enalapril is transformed into its sodium salt. The enalapril sodium salt in pharmaceutical preparations is said to be more stable than the enalapril maleate salt.

Fig.


Enalapril
decomposition
decomposition
"Enalaprilát"
"Diketopiperazin"

United States Patent no. 5.562.921 describes that the enalapril maleate salt extensively decomposes in the presence of commonly used vehicles, filling substances, lubricants or disintegrating agents in many pharmaceutical products for example in the pharmaceutical dosage forms containing microcrystalline cellulose, calcium phosphate or magnesium stearate.

It is described in EP-A-099239 and EP-B-0264887 that ascorbic acid may be used as an antioxidant or colour stabilizing agent in case of ACE-inhibitors.

The aim of our invention is to prepare pharmaceutical formulations of high stability which contain enalapril maleate with commonly used filling substances (e.g. lactose, mannitol, sorbitol) lubricant (e.g. magnesium stearate) and disintegrating agents (e.g. starch) and in which the amount of decomposition products is low even in case of long-term storage, thus ensuring a longer expiration time and in the same time a high quality.

It has been found that if enalapril maleate is transformed into pharmaceutical formulations by applying commonly used filling substance (e.g. filling substance of saccharide type) and maleic acid stabilizer, an extremely stable enalapril formulation is obtained. This is true even if magnesium stearate or other compounds are used as lubricants, affecting the stability of enalapril maleate .

At realizing our invention, we have successfully applied for example mono- or disaccharides, water-free lactose, lactose monohydrate or DC (direct compression) lactose as filling substances, starches or partly hydrolysed starches, or crospovidone (polyvinylpolypyrrolidone) as disintegrating agents, magnesium stearate, hydrogenated vegetable oil or talc as lubricants, and maleic acid as stabilizer, in addition to the currently used colouring and binding agents, e.g. ferric oxide and povidone (polyvinylpyrrolidone). Further auxiliary substances applicable for these purposes are enumerated in the Hungarian Pharmacopoeia or in the European Pharmacopoeia.

One of the preferred variant forms of our invention is the tablet or the granules for filling capsule consisting of enalapril maleate, maleic acid, lactose, starch, partly hydrolysed starch and magnesium stearate, and optionally colouring and binding agents.

Our invention also relates to the process for the preparation of the above pharmaceutical formulations. During this process, granules to be compressed in tablets or to be filled into capsules are prepared by wet granulation using aqueous solution of maleic acid.

During one of the favourable implementations of the above process, dry enalapril maleate, lactose, starch and partly hydrolysed starch are mixed, and then their mixture is granulated using aqueous solution of maleic acid used as granulation liquid. Of course, ingredients may be mixed in other sequences. The granules obtained are dried and classified, and then compressed into tablets with magnesium stearate added.

Tablets according to our invention can be prepared by direct tabletting, i.e. mixing enalapril maleate with all other auxiliary substances and with maleic acid used as stabilizing agent, and by compressing the mixture in tablets.

Pharmaceutical products (dosage forms) prepared according to our invention may preferably contain enalapril maleate in 0.1-25 weight %, lactose in 30-95 weight %, starch and partly hydrolysed starch in 6-80 weight %, maleic acid in 0.1-10 weight %, lubricant in 0.1-5 weight % and colouring and binding agents in 0.01-5 weight %.

Preferred dosage forms are tablets and granules which contain enalapril maleate in 1.5-15 weight %, lactose in 65-90 weight %, starch and/or other disintegrating agents in 5-15 weight %, binding and colouring agents in 3-7 weight %, pregelatinized starch in 1-4 weight %, maleic acid in 1-5 weight % and lubricants in 0.1-1.5 weight %. Most preferred unit dosage forms are tablets with 75-300 mg tablet mass having above preferred compositions.

Further details of our invention are shown by the examples below, without limiting our claims to the examples.

Examples

Example 1

100 g of enalapril maleate, 3930 g of lactose monohydrate, 380 g of corn starch, 120 g of pregelatinized starch were homogenized. 24 g of maleic acid was dissolved in 1000 ml of purified water. The homogenized powder mixture was granulated with slowly (10-15 min) added aqueous solution of maleic acid. The wet granules were dried (at 40-50°). The dried granules were homogenized with 20 g of magnesium stearate (for 10-20 min).

The homogenized granules were tabletted and tablets having 115 mg total mass and containing 2.5 mg of enalapril maleate were obtained.

Example 2

150 g of enalapril maleate, 5934 g of lactose monohydrate, 570 g of corn starch, 180 g of pregelatinized starch were homogenized. 36 g of maleic acid was dissolved in 1500 ml of purified water. The homogenized powder mixture was granulated with slowly (10-15 min) added aqueous solution of maleic acid. The wet granules were dried (at 40-50°). The dried granules were homogenized with 30 g of magnesium stearate (for 10-20 min).

The homogenized granules were tabletted.

Example 3

200 g of enalapril maleate, 3300 g of lactose monohydrate, 300 g of corn starch, 100 g of pregelatinized starch were homogenized. 48 g of maleic acid was dissolved in 950 ml purified water. The homogenized powder mixture was granulated by slowly (10-15 min) added aqueous solution of maleic acid. The wet granules were dried (at 40-50°). The dried granules were homogenized with 36 g of magnesium stearate (for 10-20 min).

The homogenized granules were tabletted.

Example 4

250 g of enalapril maleate, 1890 g of lactose monohydrate, 188 g of corn starch, 68 g of pregelatinized starch were homogenized. 60 g of maleic acid was dissolved in 600 ml of purified water. The homogenized powder mixture was granulated with slowly (10-15 min) added aqueous solution of maleic acid. The wet granules were dried (at 40-50°). The dried granules were homogenized with 45 g of magnesium stearate (for 10-20 min).

The homogenized granules were tabletted and tablets having 200 mg total mass and containing 20 mg of enalapril maleate were obtained.

Example 5

200 g of enalapril maleate, 3300 g of lactose monohydrate, 300 g of corn starch, 100 g of pregelatinized starch, 48 g of maleic acid were homogenized. The homogeneous powder mixture was granulated with slowly (10-15 min) added purified water (950 ml). The wet granules were dried (at 40-50°). The dried granules were homogenized with 36 g of magnesium stearate (for 10-20 min).

The homogenized mixture was tabletted.

Example 6

3300 g of lactose monohydrate, 300 g of corn starch, 100 g of pregelatinized starch were homogenized. 48 g of maleic acid was dissolved in 1100 ml of purified water. While stirring, 200 g of enalapril maleate was added. The homogeneous powder mixture was added to the suspension. The wet granules were dried (at 40-50°). The dried granules were homogenized with 36 g of magnesium stearate.

The homogenized granules were tabletted.

Example 7

250 g of enalapril maleate, 4200 g of lactose monohydrate, 370 g of corn starch, 120 g of pregelatinized starch were homogenized. 45 g of maleic acid was dissolved in 1300 ml of purified water. While stirring, 120 g of polyvinylpyrrolidone was added to the pure solution. The

homogenized powder mixture was granulated with slowly (10-15 min) added aqueous solution of maleic acid and polyvinylpyrrolidone. The wet granules were dried (at 40-50°). The dried granules were homogenized with 36 g of magnesium stearate (for 10-20 min).
The homogenized granules were tabletted.

Example 8

250 g of enalapril maleate, 60 g of maleic acid, 45 g of magnesium stearate, 120 g of polyvinylpyrrolidone, 120 g of pregelatinized starch were homogenized. 370 g of corn starch, 4200 g of lactose monohydrate were added to the homogeneous mixture and the mixture was homogenized again (for 15-20 min).
The homogeneous mixture was tabletted.

Example 9

200 g of enalapril maleate, 1600 g of lactose monohydrate, 1600 g of corn starch, 250 g of pregelatinized starch, 100 g of polyvinylpyrrolidone, 150 g of talc were homogenized. 50 g of maleic acid was dissolved in 1000 ml of purified water. The homogenized powder mixture was granulated with slowly (10-15 min) added aqueous solution of maleic acid. The wet granules were dried (at 40-50°). The dried granules were homogenized with 36 g of magnesium stearate.
The homogenized granules were tabletted.

Example 10

200 g of enalapril maleate, 250 g of pregelatinized starch were homogenized, 100 g of polyvinylpyrrolidone, 150 g of talc, 50 g of maleic acid and 40 g of magnesium stearate were homogenized. To the homogeneous mixture 1600 g of lactose and 1600 g of corn starch were added. The mixture was homogenized (for 15-20 min).
The homogenized mixture was tabletted.

Example 11

100 g of enalapril maleate, 1700 g of lactose monohydrate, 40 g of crospovidone, 110 g of maize starch and 2 g of ferrous oxide red were homogenized. 48 g of maleic acid was dissolved in 1200 ml of purified water. The homogenized powder mixture was granulated with slowly (10-15 min) added aqueous solution of maleic acid. The wet granules were dried at 40-50°C. The dried granules were homogenized with 10 g of magnesium stearate for 20 min.. The homogenized granules were tabletted and tablets having 200 mg total mass and containing 10 mg of enalapril maleate were obtained.

CLAIMS

1. Stable pharmaceutical composition, characterized in that, it contains enalapril maleate as active substance, maleic acid as stabilizing agent and one or more auxiliary substances.

2. Composition according to claim 1, characterized in that, it contains enalapril maleate in 1.5-15 weight %, filling substances in 65-90 weight %, disintegrating agents in 6-20 weight %, maleic acid in 1-5 weight %, binding and colouring agents in 3-7 weight % and lubricants in 0.1-1.5 weight %.

3. Composition according to claim 1, characterized in that, it contains mono- or disaccharides as filling substance, starches and/or crospovidone as disintegrating agent, stearate salts or esters, or hydrogenated vegetable oils as lubricants.

4. Composition according to claim 1, characterized in that, it contains enalapril maleate as active substance, maleic acid as stabilizing agent, lactose as filling substance, starch and crospovidone as disintegrating agent, magnesium stearate, hydrogenated vegetable oil or talc as lubricant, povidone as binding agent and optionally ferric oxide as colouring agent.

5. Composition according to claim 1, characterized in that, it contains enalapril maleate as active substance, maleic acid as stabilizing agent, lactose monohydrate as filling substance, starch as disintegrating agent, magnesium stearate as lubricant and optionally ferric oxide as colouring agent.

6. Composition according to claim 1, characterized in that, the dosage form is a tablet.

7. Composition according to claim 6, characterized in that, the dosage from is a tablet having 75-300 mg of tablet mass.

8. Composition according to claim 1, characterized in that, the dosage form is a capsule filled with granules.

9. Process for the preparation of composition according to claim 1, characterized in that, wet granulation is used.

10. Process according to claim 9, characterized in that, wet granulation is carried out with aqueous solution of maleic acid used as stabilizing agent.

11. Process according to claim 9, characterized in that, the enalapril maleate, lactose, disintegrating and colouring agents are mixed, dried, aqueous solution of stabilizing maleic acid is added, the mixture is wet granulated, the obtained granules are dried, classified, mixed with lubricant and compressed into tablets.

12. Use of maleic acid to stabilize enalapril maleate in a pharmaceutical composition as defined in anyone of claims 1 to 8.

13. Use of maleic acid as stabilizing agent in the manufacture of a pharmaceutical composition containing enalapril maleate as defined in anyone of claims 1 to 8.

14. Composition according to claim 1, characterized in that, it is in a commercial package in the form of orally applicable dosage form together with instructions for its administering.

INTERNATIONAL SEARCH REPORT

Ir. .ational Application No
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A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K9/20 A61K31/40 A61K47/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4 793 998 A (MURTHY KUCHI S ET AL) 27 December 1988 see abstract see column 1, line 21-27 see column 2, line 15-18 see column 3, line 34-38 see column 4, line 24 see column 4, line 43-56 see column 5, line 18-20 see column 5, line 32-41 see column 5, line 54-61 see claims 5,7,8 --- -/--	1,6,8, 12-14

[X] Further documents are listed in the continuation of box C.

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 468 929 A (SANDOZ LTD) 29 January 1992 see page 2, line 11 see page 2, line 50-53 see page 4, line 7-8 see example 5C see page 7, line 56 - page 8, line 6	1,3,5-7, 9,10, 12-14

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Information on patent family members

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